

# Phenotypic analysis of triphalangeal thumb and associated hand malformations

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## Abstract

**Triphalangeal thumb (TPT), a long, finger-like thumb with three phalanges instead of two, is regarded as a subtype of preaxial polydactyly. It can occur as a sporadic disorder, but is more often seen as a dominant familial trait. We describe four white Dutch families in which triphalangeal thumb has variable expression and is sometimes associated with preaxial extra rays, rudimentary postaxial polydactyly, cutaneous syndactyly of the hands, and, rarely, postaxial polydactyly and syndactyly of the feet. A comparison with similar familial conditions reported during the past 10 years is provided. The potential significance of linkage and molecular genetic analysis for better insight into the pathogenesis of complex hand malformations is discussed.**

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Congenital hand anomalies have a prevalence at birth of about 5 per 1000.<sup>1</sup> For The Netherlands, the best estimate is 16/10 000<sup>2</sup> (nation-wide approximately 300 affected births per year). The most frequently observed hand malformation is post- or preaxial (thumb) polydactyly with prevalences from 7 to 14 per 10 000 live births.<sup>2-4</sup>

Many attempts have been made to develop an adequate classification system for preaxial polydactyly. The most widely accepted classifications among clinicians are the two by Was-

sel<sup>5</sup> and Swanson and Brown,<sup>6</sup> both based on bone anatomy. The classification of preaxial polydactyly according to Temtamy and McKusick is widely used among clinical geneticists and defines the following subtypes.<sup>7</sup>

Type I preaxial polydactyly which comprises various degrees of duplication of bi-phalangeal thumbs. It is usually sporadic, unilateral, and not associated with thenar anomalies. Type II and type III are two different forms of triphalangeal thumbs, opposable and non-opposable, respectively. Type IV (polysyndactyly) is usually associated with foot anomalies and resembles the type of limb deformity seen in Greig cephalopolysyndactyly syndrome.

Preaxial polydactyly can occur as an isolated anomaly or as part of several complex congenital malformation syndromes. The defect may be unilateral or bilateral, and hands or feet or both may be affected. Sporadic as well as familial occurrence has been described, with autosomal dominant inheritance the most likely mode of transmission.<sup>8</sup>

Triphalangeal thumb (TPT), a long, finger-like thumb with three phalanges instead of two, is usually regarded as a subtype of preaxial polydactyly. Lapidus *et al*<sup>9</sup> reported the prevalence of TPT as 1/25 000. In the series from Iowa University, TPT represented 3% of congenital malformations of the upper extremities.<sup>10</sup> TPT is occasionally seen as a sporadic disorder, but more often as an autosomal dominant familial trait. It is therefore probable that the overall prevalence of this disorder is very low in large populations, but may peak in areas with affected families.

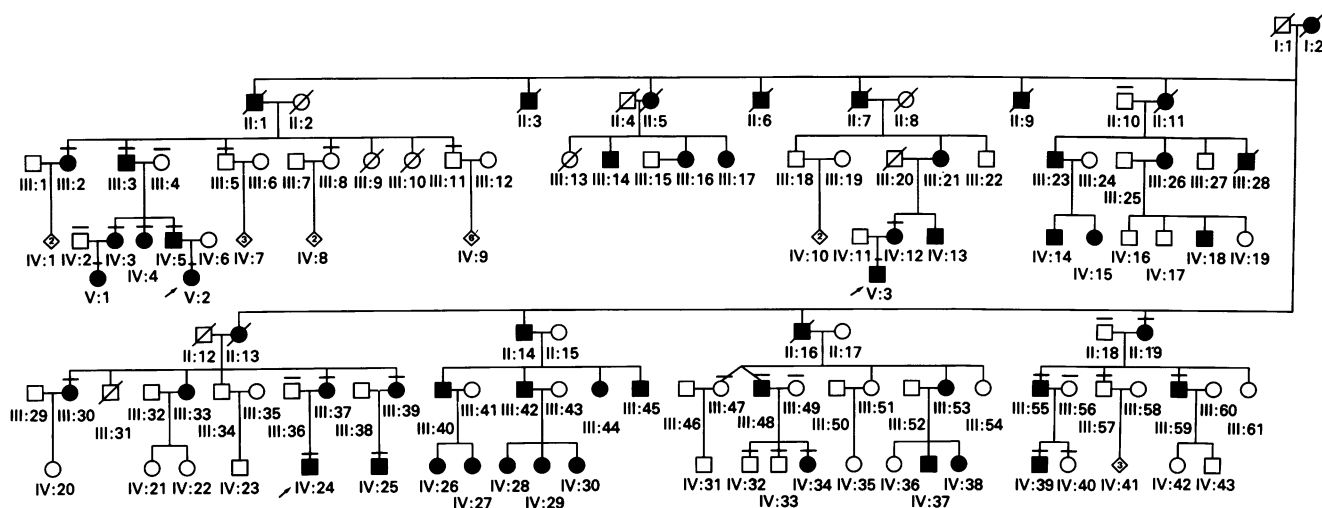


Figure 1 Family A. Three initial probands are indicated by arrows. [—] indicates that the family member was examined by one of the authors personally.

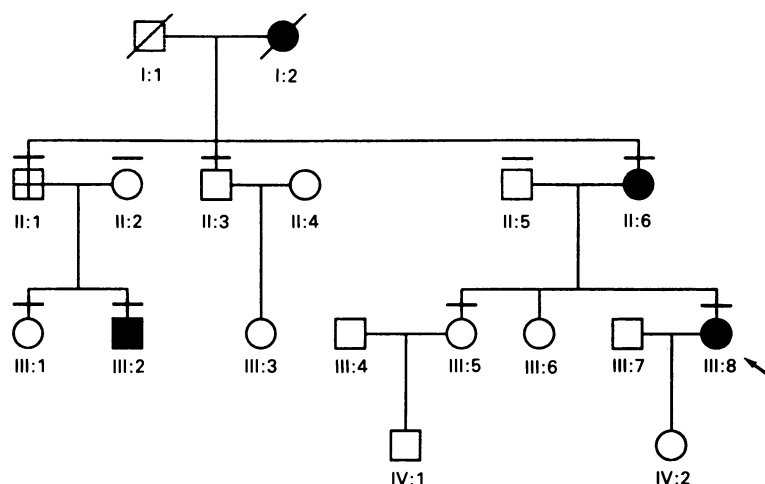


Figure 2 Family B. Proband is indicated by an arrow. — indicates that the family member was examined by one of the authors personally. II:1 had only unilateral rudimentary postaxial polydactyly of the hand (see text for further description and discussion about variable expression and reduced penetrance).

Recently, we identified 11 possibly related probands and their families (white Dutch), in which the expression of thumb anomalies ranged from an opposable triphalangeal thumb to a triphalangeal index-like digit instead of a thumb, including two extra hypoplastic rays on the radial side of the 'thumb' (septadactyly).

In this paper we describe our findings in the families of six of these 11 probands with respect to pattern of inheritance and variability of clinical phenotype, function, and morphology. A comparison with similar conditions reported during the past 10 years is provided. The usefulness of the currently available classifications and the potential significance of gene localisation and identification in order to understand the pathogenesis of complex hand malformations will be discussed.

#### Patients, materials, and methods

Through a review of medical records of the Department of Plastic and Reconstructive Surgery of the Academic Hospital Rotterdam-Dijkzigt/Sophia concerning patients with congenital hand malformations, we ascertained 11 probands with TPT, all of whom had been referred for primary or secondary plastic surgery. The review covered a period of referrals from 1983 to 1991. Each of these 11 probands had a strikingly similar phenotype, a strongly positive family history of similar hand malformations suggestive of autosomal dominant inheritance, and all their parents originated from a demographically and geographically small region in the south west part of The Netherlands. This raised the possibility that all the patients and their affected relatives might have

the same genetic disorder. Therefore we initiated a clinical genetic and genealogical investigation, in collaboration with one of the family practitioners of this community (PS).

The families of the 11 probands were contacted through the family practitioner and one of us (JZ) with a request for cooperation in the investigation. Full written information about the protocol was provided and informed consent was obtained from each participant. The research protocol was approved by the Medical Ethics Committee of the Erasmus University Rotterdam and Academic Hospital Rotterdam (Project no 92.1031).

Standardised forms were used for the following. (1) Medical history of each participant including a checklist for teratogenic exposure during pregnancy, congenital anomalies, and previous surgery. (2) Family history of each affected/unaffected relative, maternal and paternal, including a checklist for parental consanguinity, congenital malformations, hereditary or chronic diseases; family histories from different members of the same family were cross checked to increase the validity of the information and supplemented with available photographs on which hand morphology of the ancestors was verified. (3) Physical examination, including a checklist for general and specific abnormalities of the hands and feet and craniofacial malformations.

In principle, both parents of each patient underwent complete examination in order to evaluate the possibility that a patient might have inherited the putative gene defect from the spouse of the affected parent or from both parents.

Persons were regarded as affected when the following criteria were fulfilled. (1) Triphalangeal thumb or biphalangeal partly duplicated thumb alone, or in combination with any of the following: preaxial extra ray or postaxial polydactyly type B or both; syndactyly between digits III/IV/V. A person displaying postaxial polydactyly only was not considered to be affected.

All patients were seen by one of us (JZ). Ten patients and 10 apparently unaffected first degree relatives were also seen by a clinical geneticist (DL), in order to evaluate the possibility that TPT was part of a more complex malformation syndrome. Clinical photographs were taken and reviewed of most of the patients (DL, JZ). In addition, the registry of the Clinical Genetics Centre Rotterdam covering the south west region of The Netherlands was screened for potentially related congenital malformations diagnosed in patients from this area.

#### Results

According to the family histories, 186 out of a total of 346 subjects were presumed affected and 160 presumed unaffected, with a sex ratio among affected subjects of 91/95 (M/F).

We have so far had the opportunity to examine the families of six of the 11 probands. By means of genealogical studies we were able to link the families of three of these probands

Table 1 Parent-offspring couples by gender combinations among present families

	Family A	Family B	Family C	Family D	Subtotal
Male to male	2	4	4	1	11
Male to female	1	5	6	0	12
Female to male	7	3	4	1	15
Female to female	9	5	6	2	22
Subtotal	19	17	20	4	60

and their affected relatives to one another. These three interrelated families will be referred to as family A (fig 1). The ancestors of the other probands all originated from the same village. One hundred and twenty four

subjects from the four families of the six probands have been personally examined by the investigators; 60 persons out of this group were affected, 38 were unaffected, and 26 were (healthy) partners of affected subjects.

Among the couples examined, there was no known consanguinity. The inheritance pattern is clearly autosomal dominant with almost complete penetrance. The variability of the expression of this disorder could not be related to the sex of the subject or the sex of the affected transmitting parent. Male to male transmission was observed in 11 out of 60 affected parent-child pairs (table 1).

The phenotype varied between the following two extremes. Subject X, aged 41, had an ulnar deviation in the interphalangeal joint of both her thumbs, because of an extra delta shaped phalanx. Thenar musculature was normally developed as was the first web. She had normal opposition function in both hands.

Her son, subject Y, aged 21, had bilateral triphalangeal index-like digits instead of normal thumbs, both in the same plane as the other digits. Additional hypoplastic digits were present in both hands. They resembled rudimentary thumbs and were surgically removed at an early age. The maximum distance between the distal finger pads of the "thumb" and the index finger was only 5 cm in both hands, indicative of a severe narrowing of the first web. The thenar muscles of both hands were hypoplastic. This patient was only capable of "pseudo-opposition", performed by the adductor and both flexor muscles of the thumb. Both hands showed full cutaneous syndactyly between digits IV and V. In both fifth digits there was rudimentary postaxial polydactyly. He also had cutaneous syndactyly between his fourth and fifth toes on both feet. No photographs of this patient are shown because he had just undergone the fifth operation on his hands at the time we saw him.

The expression in most other patients varied between these two extreme forms. A feature common to all patients was the presence of a triphalangeal thumb. A delta shaped extra phalanx was usually associated with less severe thenar hypoplasia, normal first web, normal position of the thumb, and good thumb function. A rectangular extra phalanx (index-like thumb) was often associated with more severe thenar hypoplasia, narrow first web, thumb in the same plane as the other digits, and defective opposition.

On x ray examination, thumbs with a delta shaped extra phalanx usually showed at least one sesamoid bone at the level of the metacarpophalangeal joint, suggesting the presence and development of at least some thenar muscles, whereas thumbs with a rectangular extra phalanx had a digit-like appearance, usually without sesamoid bones (figs 3-5). In both types of TPT the epiphysis of the first metacarpal was seen either distally or proximally, and sometimes on both sides.

Most subjects were symmetrically affected, sometimes with small differences in expression only, for example in the degree of thenar hypoplasia, the presence or absence of pre- or

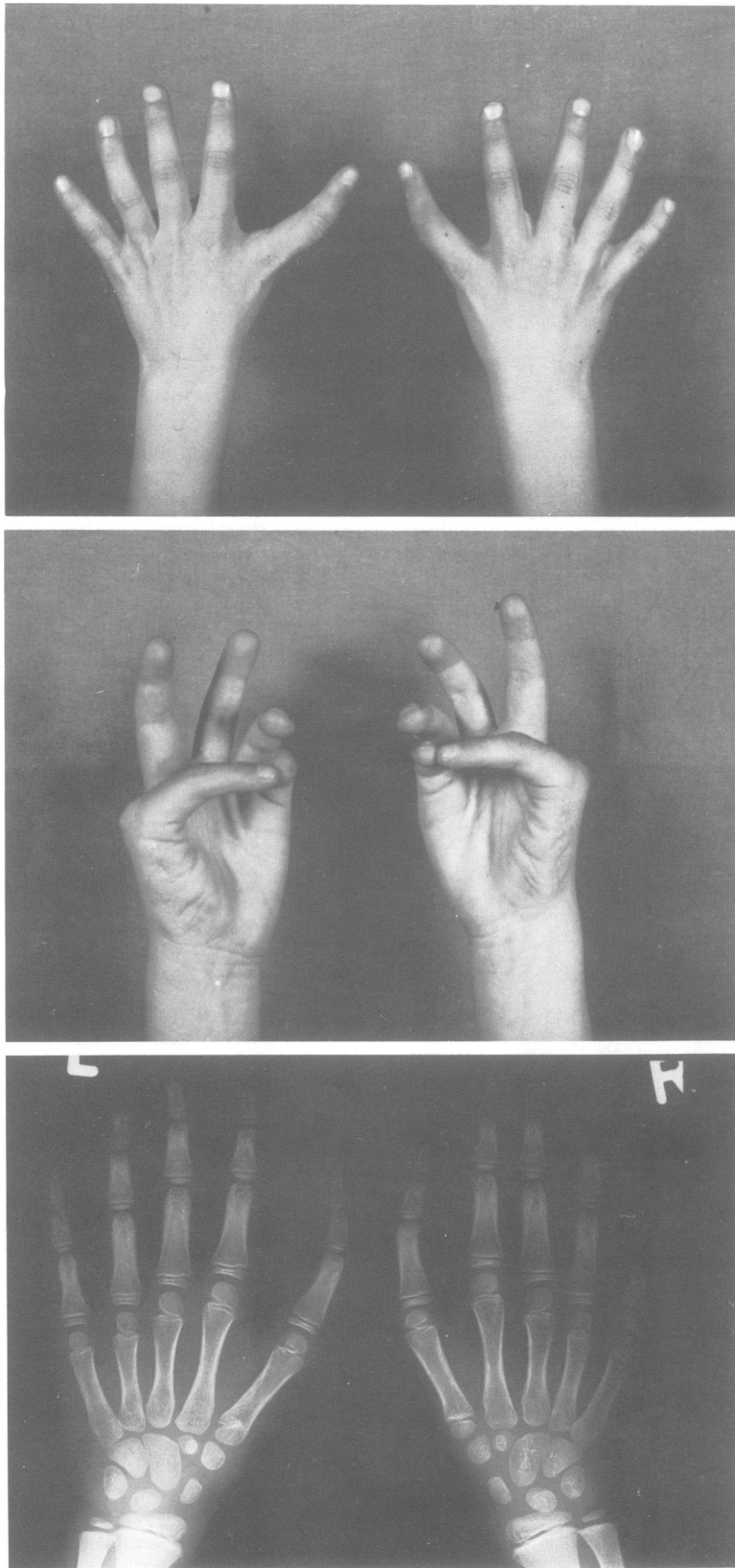


Figure 3 Photographs and x ray of the hands of proband 1, aged 7, after amputation of the preaxial extra rays, correction of cutaneous syndactyly between digits IV and V of the left hand, and before thumb surgery. Notice the index-like appearance of the thumb, the narrow first web space, pseudo-opposition, hypoplastic thenar muscles, and, on the x ray, the absence of the sesamoid bones and two epiphyses of the first metacarpal.

postaxial polydactyly or both, the degree of syndactyly, or duplication of the fifth toe.

In only one person (subject II-1 from family B, fig 2) was there a discrepancy between the phenotype and the genotype as derived from information from the pedigree. This male,

aged 55 years, had an affected mother as well as affected offspring. On examination, he had only a rudimentary postaxial polydactyly on his left hand in the form of a wart with a diameter of 3 mm on the lateral border of his middle phalanx. No other abnormalities were found.

The clinical findings in our families are summarised in table 2.

### Discussion

The families described here show a consistent phenotype of opposable or non-opposable TPT, and varying expressions of extra radial ray(s), rudimentary postaxial polydactyly, and cutaneous syndactyly. All initially identified probands originated from the same geographically and demographically small region and the families of three of them could be linked to one another, suggesting a common gene mutation.

The pattern of inheritance is clearly autosomal dominant with (almost) complete penetrance and variable expression, and without evidence for imprinting. The male to female ratio is almost equal to one. Table 1 shows that the transmitting parent was more often female than male. This can be explained by the fact that in three out of four families, the transmitting parent of the oldest generation was a female with a much larger number of offspring than in subsequent generations.

According to our present diagnostic criteria, patient II-1 from family B (fig 2) was not affected, showing no clinical or radiographical signs of TPT. However, in the pedigree he was an obligate TPT gene carrier, implying that the penetrance of the TPT gene is not 100% but slightly less, with postaxial polydactyly in patient II-1 from family B as a coincidental finding. Alternatively we have to consider isolated postaxial polydactyly as a forme fruste expression of this gene mutation. Future studies on more families with TPT may clarify this question.

In the past, several other families with TPT and associated hand malformations similar to those observed in our families have been reported.<sup>11-18</sup> However, none of these clinical phenotypes completely correspond to one another or to ours. There are remarkable differences with respect to the severity of each symptom as well as their frequency among affected subjects. In table 3, the clinical phenotypes of five families reported during the past 10 years are compared with one another and with the families reported in this paper.

In the family described by Merlob *et al.*,<sup>15</sup> the three family members examined had an opposable TPT, which in two of the members was associated with duplication of the big toes. This phenotype, apart from the absence of preaxial extra rays, is very much like the phenotype in an Indian family reported by Radhakrishna *et al.*<sup>12</sup> It included TPT, preaxial (radial) extra ray, and duplication of the big toes. Particularly, the latter malformation was not observed in any of 60 affected subjects of our families. The fact that preaxial extra rays in the hands was not observed in the family of

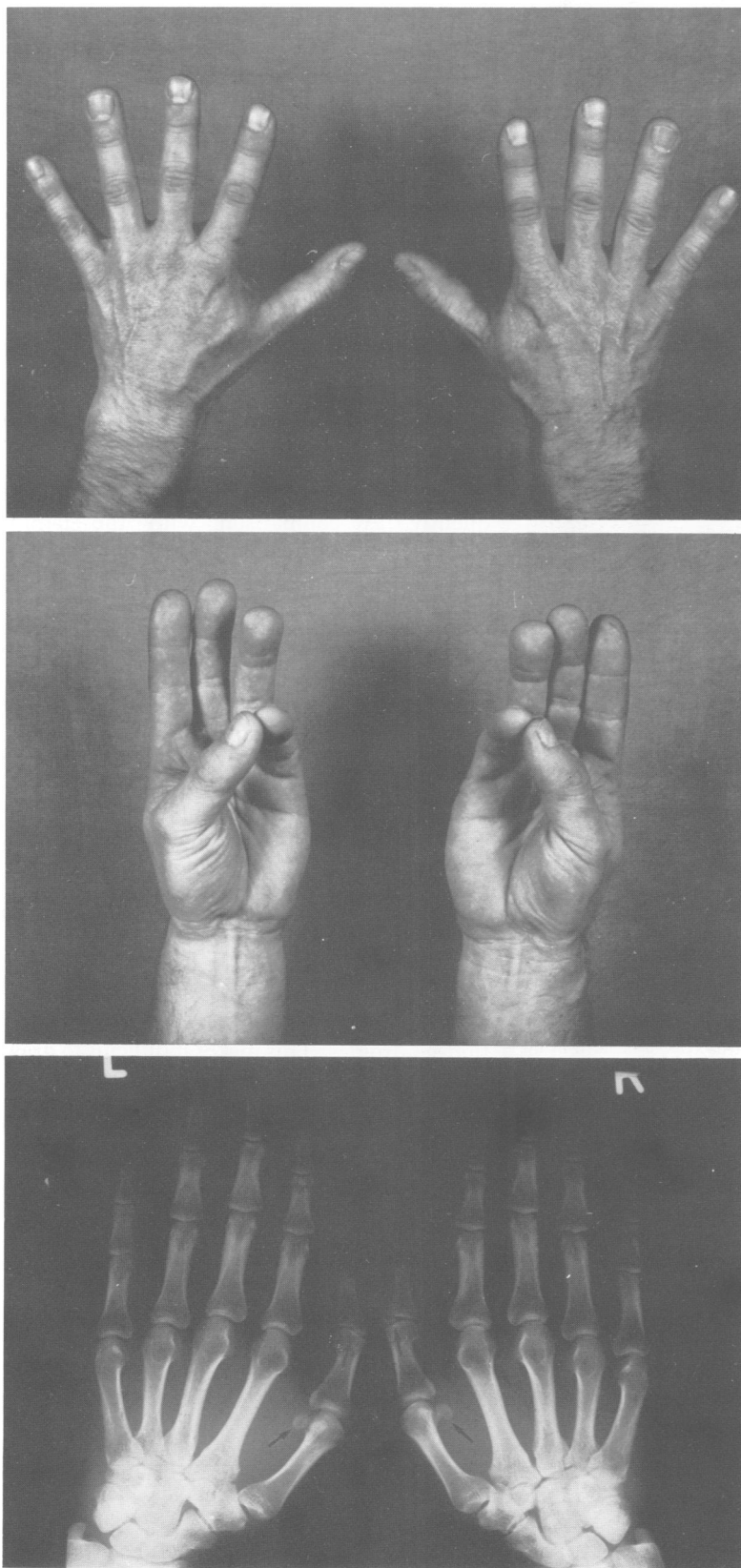


Figure 4 Photographs and x ray of the hands of the uncle of proband 1 showing slight ulnar clinodactyly in the interphalangeal joints of the thumbs, almost normal thenar muscles, and normal opposition, and, on the x ray, sesamoid bones and two small delta phalanges in both thumbs (arrows).

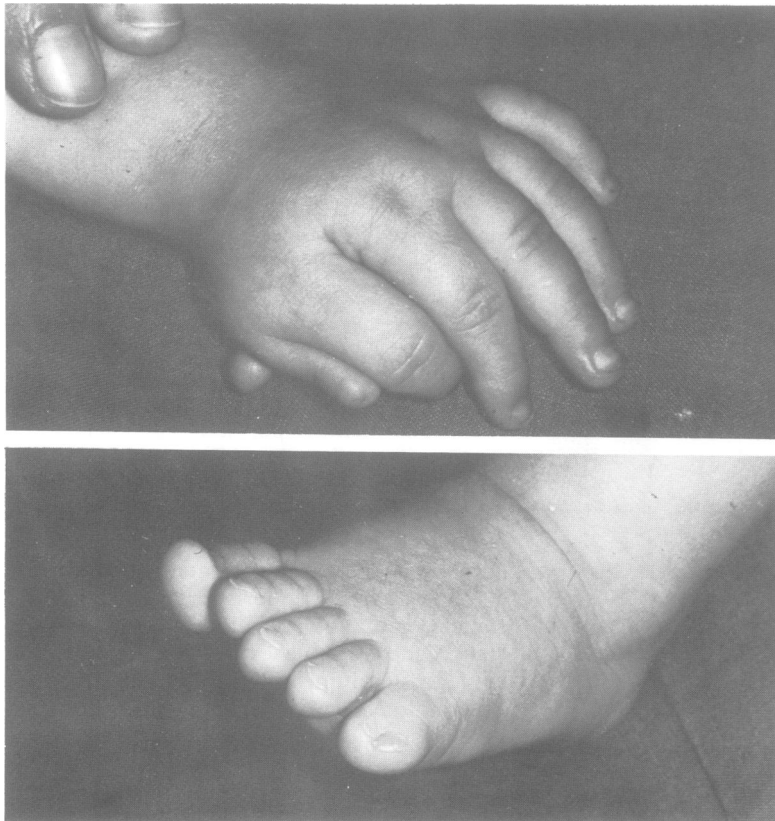


Figure 5 Photographs of the left hand and foot of proband 2, aged 15 months, before surgery, showing index-like triphalangeal thumb with two hypoplastic preaxial extra rays and duplication of the fifth toe.

Table 2 Phenotype analysis of present families

	Family A	Family B	Family C	Family D	Total
TPT	19/19	17/17	20/20	3/4	59/60
Thenar hypoplasia	13/19	17/17	17/20	2/4	49/60
Preaxial extra ray	11/19	16/17	14/20	2/4	43/60
Postaxial polydactyly	9/19	8/17	10/20	1/4	28/60
Syndactyly	2/19	2/17	0/20	1/4	5/60
Postaxial foot polydactyly	1/19	1/17	0/20	0/4	2/60
Foot syndactyly (IV-V)	1/19	1/17	0/20	0/4	2/60

In family D subject II-1 who only had rudimentary postaxial polydactyly is included in the patient denominator assuming that he is an obligate carrier of the TPT gene in view of TPT in his mother and his son. For further description see text.

Table 3A Qualitative phenotypic comparison of present and previously reported families

	Merlob <i>et al</i> <sup>15</sup>	Nicolai <i>et al</i> <sup>11</sup>	Warm <i>et al</i> <sup>14</sup>	Miura <i>et al</i> <sup>13</sup>	Radhakrishna <i>et al</i> <sup>12</sup>	Present cases
TPT	+++	++	+++	+++	+++	+++
Thenar hypoplasia	—	+	+++	++	?	+++
Preaxial extra ray	—	++	++	++	+++	++
Postaxial polydactyly	—	++	—	+++	—	++
Syndactyly	—	+++	—	++	—	+
Preaxial foot polydactyly	++	—	—	+	++	—
Postaxial foot polysyndactyly	—	+	—	—	—	+

— absent, + present, ++ prominent, +++ predominant feature.

Table 3B Quantitative phenotypic comparison of present and previously reported families

	Merlob <i>et al</i> <sup>15</sup>	Nicolai <i>et al</i> <sup>11</sup>	Warm <i>et al</i> <sup>14</sup>	Miura <i>et al</i> <sup>13</sup>	Radhakrishna <i>et al</i> <sup>12</sup>	Present cases
TPT	3/3	2/7	3/3	2/2	2+/71	59/60
Thenar hypoplasia	0/3	2/7	2/3	2/2	2+/71	49/60
Preaxial extra ray	0/3	7/7	3/3	1/2	61/71?	43/60
Postaxial polydactyly	0/3	7/7	0/3	2/2	0/71	28/60
Syndactyly	0/3	7/7	0/3	2/2	0/71	5/60
Preaxial foot polydactyly	2/3	0/7	0/3	1/2	21/71?	0/60
Postaxial foot polysyndactyly	0/3	2/7	0/3	0/2	0/71	4/60

No of patients with indicated symptom/No of patients examined by reporting authors.

Merlob *et al*<sup>15</sup> may be the result of chance since they only reported three affected relatives.

Warm *et al*<sup>14</sup> described a family with non-opposable TPT, which in two out of three family members was associated with a preaxial extra ray. The phenotype is compatible with that of our families, even though Warm *et al*<sup>14</sup> did not observe postaxial polydactyly, syndactyly, or postaxial polydactyly of the feet, since this may have been the result of chance. These three features were observed only infrequently in our patients, and their family report consisted of only three examined affected subjects.

Nicolai and Hamel<sup>11</sup> and Miura *et al*<sup>13</sup> reported families with complex hand anomalies consisting of syndactyly, polydactyly, and TPT, resembling Haas's malformation. These two families and the presently reported four families share the same characteristics, but, apart from a triphalangeal thumb, there is a clear difference with respect to the most predominant symptom. Severe syndactyly and postaxial polydactyly were noted in all of the seven patients described by Nicolai *et al*,<sup>11</sup> whereas these malformations were much milder in our families and observed infrequently. A comparison with the family reported by Miura *et al*<sup>13</sup> is hampered by the small size of their family, but it is remarkable that preaxial polydactyly of the foot was present in one of their two patients, but was not observed in any of our 60 patients.

The classification of congenital hand malformations is usually based on clinical appearance or skeletal morphology but is frequently complicated by the coexistence of different types of malformations, like polydactyly, syndactyly, and thumb hyperphalangism in the TPT families discussed here. Usually the most prominent or most frequent malformation is used as a lead for classification of complex malformations. However, the application of the currently available classification systems is complicated by the large variation in expression and the considerable overlap between apparently different complex hand malformation syndromes. This makes it difficult to draw conclusions about the extent of genetic heterogeneity among the previously and currently reported TPT families. Nevertheless, the fact



that the phenotypic spectrum is very consistent among our currently reported four families, together with their common geographical and demographic origin, strongly supports the hypothesis that all affected subjects examined by us so far share the same genetic defect.

Although the differences in pattern of expression between the currently and previously reported families could be explained by genetic (allelic or locus) heterogeneity, the variable expression within each family indicates the role of additional genetic or environmental factors. This suggests that the TPT gene is a regulatory gene involved in the development of the hand during embryogenesis. Localisation of the disease gene(s) by positional cloning strategies and identification of the gene(s) involved and the mutations causing TPT will help to answer these questions and may contribute to the establishment of a new aetiological and pathogenetic classification of complex hand malformations, as a supplement to current morphological classifications.

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